Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Currently Amended) A pharmaceutical composition for use in inhibiting growth of cancer cells in a mammalian subject, said composition comprising

a urease enzyme, and,

associated with said enzyme, a chemical entity effective to enhance the delivery of the enzyme to cancer cells, when the composition is administered to the subject.

2. (Original) The composition of claim 1, wherein said chemical entity includes a hydrophilic polymer (i) conjugated to the urease, (ii) selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, polyvinylmethylether, polyhydroxypropyl methacrylamide, polyhydroxypropyl methacrylate, polyhydroxyethyl acrylate, polymethacrylamide, polydimethylacrylamide, polymethyloxazoline, polyethyloxazoline, polyhydroxyethyloxazolione, polyhydroxypropyoxazoline, polyaspartamide, and hydrophilic cellulose derivatives, and (iii) present in an amount effective to extend the blood circulation time or reduce the antigenicity of said composition relative to native urease.

3. (Original) The composition of claim 2, wherein said hydrophilic polymer is polyethylene glycol having a molecular weight between about 1,000 and 10,000 daltons.

4. (Original) The composition of claim 1 or 2, wherein said chemical entity is a targeting moiety attached to said urease and selected from the group consisting of an anti-tumor antigen antibody, anti-hCG antibody, and a ligand capable of binding specifically to cancer-cell surface receptors.

5. (Original) The composition of claim 4, wherein said targeting moiety is a polypeptide, and said composition is a fusion protein of the targeting moiety and urease enzyme.

6. (Original) The composition of claim 4, wherein said urease includes, at its C- or N-terminus, a first coil-forming peptide characterized by a selected charge and an ability to interact with a second, oppositely charged coil-forming peptide to form a stable α-helical coiled-coil heterodimer; and said chemical entity includes a targeting moiety which includes said second coil-forming peptide.

7. (Original) The composition of claim 1, wherein said chemical entity includes vesicles having urease enzyme in entrapped form.

8. (Original) The composition of claim 7, wherein said vesicles are liposomes which are long-circulating by virtue of an exterior coating of polyethylene glycol chains, and sized to extravasate into tumor regions, when the composition is administered intravenously.

9. (Original) The composition of claim 7, wherein said vesicles are liposomes having surface bound targeting moieties selected from the group consisting of an anti-tumor antigen antibody, anti-hCG antibody, and ligands capable of binding specifically to cancer-cell surface receptors.

10. (Original) The composition of claim 1, wherein said chemical entity includes a urease inhibitor associated therewith, in an amount sufficient to inhibit the activity of said enzyme.

11. (Original) The composition of claim 1, wherein said urease is a plant or bacterial urease.

12. (Original) The composition of claim 1, further comprising an agent selected from the group consisting urea, a therapeutically active anti-tumor agent and an imaging agent.

13. (Original) The composition of claim 12, which further includes vesicles containing the urease and agent in entrapped form.

14. (Withdrawn) A method for inhibiting growth of cancer cells in a mammalian subject, comprising
exposing the cells to urease, in an amount of urease effective to inhibit growth of the cancer cells.

15. (Withdrawn) The method of claim 14, wherein the cancer cells comprise a solid tumor, and said exposing includes injecting the urease directly into the tumor of the subject.

16. (Withdrawn) The method of claim 15, wherein said exposing includes visualizing said tumor with an image-guidance tool selected from the group consisting of ultrasound, fluoroscopy, MRI, positron emission tomography.

17. (Withdrawn) The method of claim 15, which further includes, following said exposing, (i) interrogating the subject with a diagnostic tool capable of detecting changes in extracellular pH is a subject's tissue, (ii) identifying a tissue region within the subject that shows a selected elevation in extracellular pH following said administering, and (iii) based on said identifying, repeating said exposing until a selected change in extracellular pH within the entire solid tumor is achieved.

18. (Withdrawn) The method of claim 14 wherein the cancer cells comprise a solid tumor, and said exposing includes administering urease parenterally to the subject other than by direct injection.

19. (Withdrawn) The method of claim 15 or 18, wherein said urease is derivatized with a hydrophilic polymer (i) selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, polyvinylmethylether, polyhydroxypropyl methacrylamide, polyhydroxypropyl methacrylate, polyhydroxyethyl acrylate, polymethacrylamide, polydimethylacrylamide, polymethyloxazoline, polyethyloxazoline, polyhydroxyethyloxazolione, polyhydroxypropyoxazoline, polyaspartamide, and hydrophilic cellulose derivatives, and (ii) present in an amount effective to extend the blood circulation time or reduce the antigenicity of said composition relative to native urease.

20. (Withdrawn) The method of claim 19, wherein said hydrophilic polymer is polyethylene glycol having a molecular weight between about 1,000 and 10,000 daltons.

21. (Withdrawn) The method of claim 18, which further includes, following said exposing, (i) interrogating the subject with a diagnostic tool capable of detecting changes in extracellular pH is a subject's tissue, (ii) identifying a tissue region within the subject that shows a selected elevation in extracellular pH following said administering, and (iii) based on said identifying, repeating said exposing until a selected change in extracellular pH within the entire solid tumor is achieved.

22. (Withdrawn) The method of claim 14, wherein urease has attached thereto, a targeting moiety selected from the group consisting of an anti-tumor antigen antibody, anti-hCG antibody, and a ligand capable of binding specifically to cancer-cell surface receptors, and said exposing includes administering the urease composition parenterally to the subject.

23. (Withdrawn) The method of claim 22, wherein said urease includes, at its C- or N-terminus, a first coil-forming peptide characterized by a selected charge and an ability to interact with a second, oppositely charged coil-forming peptide to form a stable α-helical coiled-coil heterodimer; and said targeting moiety includes said second coil-

forming peptide, and said exposing includes administering the urease composition parenterally to the subject.

24. (Withdrawn) The method of claim 14, wherein said urease is entrapped within vesicles, and said exposing includes administering the vesicles composition parenterally to the subject.

25. (Withdrawn) The method of claim 24, wherein said liposomes are long-circulating by virtue of an exterior coating of polyethylene glycol chains, and sized to extravasate into tumor regions, when the composition is administered parenterally, and said exposing includes administering the liposomes parenterally to the subject other than by direct injection.

26. (Withdrawn) The method of claim 14, wherein said urease is complexed with a urease inhibitor, and said exposing comprises administering to the subject, a complex of the urease and urease inhibitor.

27. (Withdrawn) The method of claim 14, which further includes, following said exposing, of modulating the activity of urease on cancer cells by administering to the subject, an amount of a urease inhibitor effective to reduce the activity of urease on said cancer cells.

28. (Withdrawn) The method of claim 14, wherein said exposing comprises administering to the subject
a first conjugate comprising a tumor targeting moiety and a first binding moiety having an ability to interact with a second binding moiety; and
a second conjugate comprising the second binding moiety conjugated with urease.

29. (Withdrawn) The method of claim 28, wherein the first binding moiety comprises a first coil-forming peptide characterized by a selected charge and an ability to interact with a second, oppositely charged coil-forming peptide to form a stable α-

helical coiled-coil heterodimer; and the second binding moiety comprises the second coil-forming peptide.

30. (Cancelled) The method of claim 14 wherein said exposing comprises

administering to the subject, a gene therapy composition comprising

a targeting vector effective, when administered to the subject, of selectively transfecting cancer cells, and

carried in said vector, a recombinant nucleic acid sequence effective to produce a urease mRNA in transfected cancer cells.

31. (Cancelled) The method of claim 30, wherein said vector is an adenovirus.

32. (Cancelled) The method of claim 30, wherein said nucleic acid sequence encodes urease and a secretory leader sequence effective to promote secretion of the urease from the transfected cancer cells.

33. (Cancelled) The method of claim 14, which further includes administering urea to the subject.

34. (Cancelled) In a subject having a solid tumor a method of enhancing the therapeutic efficacy of a weakly basic anti-tumor compound whose effectiveness is reduced by a higher intracellular/lower extracellular pH gradient in a solid tumor, comprising

administering to the subject receiving said anti-tumor compound, an amount of urease effective to reduce or reverse the higher intracellular/lower extracellular pH gradient in a solid tumor.

35. (Cancelled) The method of claim 34, wherein said anti-tumor compound is selected from the group consisting of doxorubicin, daunorubicin, mitoxanthrone, epirubicin, mitomycin, bleomycin, vinca alkaloids such as vinblastine and vincristine, alkylating agents such as cyclophosphamide and mechlorethamine hydrochloride, and antrineoplastic purine and pyrimidine derivatives.

36. (Cancelled) The method of claim 34, wherein said administering is effective to raise the extracellular fluid of the tumor to at least pH 7.2.

37. (Cancelled) The method of claim 34, wherein said administering includes injecting urease directly into the subject's tumor.

38. (Cancelled) The method of claim 34, wherein said urease is administered parenterally other than by direct injection in a composition that includes a chemical entity effective to enhance the delivery of the enzyme to a solid tumor.

39. (Withdrawn) A method of assessing the presence, size or condition a solid tumor in a subject, comprising

administering urease to the subject containing, or suspected of containing, a solid tumor, under conditions effective to localize the urease in a solid tumor in the subject, interrogating the subject with a diagnostic tool capable of detecting changes in extracellular pH is a subject's tissue, and

identifying a tissue region within the subject that shows an elevation in extracellular pH following said administering.

40. (Withdrawn) The method of claim 39, wherein said interrogating includes administering to the subject a pH-sensitive diagnostic agent capable of localizing in a tumor, and interrogating the subject with a diagnostic tool effective to detect said agent.

41. (Withdrawn) The method of claim 39, wherein said interrogating includes performing an MRI scan on the subject.

42. (Withdrawn) The method of claim 39, wherein administering urease to the subject is employed in an anti-tumor therapy, and said identifying is used for detecting the localization of urease in a solid tumor.

43. (Withdrawn) The method of claim 42, wherein said identifying is used for monitoring the change in size and shape of the tumor in response to urease administration.

44. (Cancelled) A kit for use in inhibiting growth of cancer cells in a mammalian subject, said kit comprising

a pharmaceutical composition containing urease enzyme, and

instructional materials teaching the administration of the composition to a subject, for the treatment of a cancer in the subject.

45. (Cancelled) The kit of claim 44, wherein said instructional material teaches administering the urease composition to a subject in an amount which is dependent on the size of the tumor and between 0.1 to 100 international units urease activity per mm^3 tumor, when the composition is administered by direct injection into the tumor, and in an amount between 100-100,000 international units/kg international units urease activity/kg subject body weight, when the composition is administered parenterally to the subject other than by direct injection into the tumor.

46. (Cancelled) The kit of claim 44, wherein said instructional material teaches administering the urease composition to a subject who is also receiving a weakly basic anti-tumor compound whose effectiveness is reduced by a higher intracellular/lower extracellular pH gradient in a solid tumor, in an amount of urease effective to reduce or reverse the higher intracellular/lower extracellular pH gradient in a solid tumor.

47. (Cancelled) The kit of claim 44, wherein said instructional material teaches administering the urease composition to a subject containing, or suspected of containing, a solid tumor, under conditions effective to localize the urease in a solid tumor in the subject, interrogating the subject with a diagnostic tool capable of detecting changes in extracellular pH is a subject's tissue, and identifying a tissue region within the subject that shows an elevation in extracellular pH following said administering.

48. (Cancelled) A gene therapy composition for use in inhibiting growth of cancer cells in a mammalian subject, comprising

a targeting vector effective, when administered to the subject, of selectively transfecting cancer cells, and

carried in said vector, a recombinant nucleic acid sequence effective to produce a urease mRNA in transfected cancer cells.

49. (Cancelled) The composition of claim 48, wherein said vector is an adenovirus.

50. (Cancelled) The gene therapy composition of claim 48, wherein said sequence encodes urease and a secretory leader sequence effective to promote secretion of the urease from the transfected cancer cells.